REMARKS

Claims 1-52 are pending. Claims 13-52 are withdrawn from consideration. Claims 1-12 have been examined in the present Office Action and have been rejected under 35 U.S.C. § 112, first and second paragraphs. Each of these rejections is addressed below.

Support for the Amendments

The specification has been amended to delete the phrase "in two panels" from the description of Figure 7 (line 7, page 35) to correctly identify Figure 7 as filed.

The specification has also been amended to clarify that "*mSal2*" is murine Sal2. Applicants note that support for this amendment can be found throughout the specification. For example, on page 3 (lines 28 and 29), the statement "a knockout mouse featuring a knockout mutation in a genomic *mSal2* gene" clearly identifies the letter "m" as meaning "murine" as opposed to "mutant" *Sal2*. Further support for this amendment may be found, for example, on page 5 (line 15 and line 27), page 12 (line 27), page 15 (line 11), page 23 (line 24), and page 24 (line 30).

Claim 1 has been amended to recite a method to identify a mammal having or at risk of acquiring a proliferative disease, by performing at least one of the following steps: 1) measuring Sal2 protein levels in a cell of a mammal relative to the Sal2 protein level in a mammal not having or being at risk of having a proliferative disease; 2) determining the presence or absence of an altered Sal2 protein in the mammal relative to a Sal2 protein in a mammal not having or being at risk of having a proliferative disease; or 3) determining the presence or absence of a proliferative disease-associated alteration in a *Sal2* nucleic acid in the mammal relative the nucleic acid sequence of SEQ ID NO. 2 and SEQ ID NO.:4. According to the present invention, a decrease in Sal2 protein levels, the presence of an altered Sal2 protein, or the presence of an alteration in the *Sal2* nucleic acid identifies a mammal as having or being at risk of acquiring a proliferative disease.

Support for this claim amendment may be found, for example, on page 20 (lines 30 and 31), Figure 7, Table 3, and on page 36 of the specification.

Claim 7 has been amended to clarify the claim language. Support for this amendment can be found throughout the specification, for example, on page 3 (lines 5-11), on page 19 (lines 1-7), and on page 36 (lines 11-28).

No new matter has been added by any of the present amendments.

Summary of the Invention

The current invention features methods for diagnosing and treating patients having or being at risk of acquiring a proliferative disorder, such as cancer. These methods involve measuring the Sal2 protein level in a cell relative to the Sal2 protein levels in a mammal not having or being at risk of acquiring a proliferative disease, determining the presence or absence of an altered form of a Sal2 protein relative to a Sal2 protein in a mammal not having or being at risk of acquiring a proliferative disease, or determining the presence or absence of a proliferative disease-associated alteration in a *Sal2* nucleic acid relative to the sequence of SEQ ID NO.:2 or 4. Since many cancers, including ovarian cancer, do not present obvious symptoms, tumors in patients are often undetected. This results in high mortality rates. When detected, tumors are often in advanced and late stages and patients bearing such tumors are often insufficiently responsive to standard anti-cancer therapies, the result being death of the patient. The screening methods of the present invention are particularly useful in the early diagnosis of cancer risk, at a time when the cancer can often be treated.

Rejections under 35 U.S.C. § 112, first paragraph

Written Description

Claims 1-12 stand rejected under 35 U.S.C. § 112, first paragraph, as being supported by an inadequate written description. The Examiner argues that, aside from the disclosed genetic alteration resulting in the substitution of a serine residue for a proline residue at amino acid position 73(S73C), the specification fails to provide evidence of additional genetic alterations in a tumor or a proliferative disorder. The Examiner therefore asserts that the disclosed mutation is not a representative species of the genus of altered *Sal2* nucleic acid molecules encompassed by the claims by failing to teach any structure, identifying characteristics and structure-function relationship of the genus.

In particular, the Examiner states that:

> "...a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of *altered Sal2* that are "associated with a proliferative disease". Therefore, only the described substitution of a Cys for the Ser at position 73 of ESQ. [*sic*] ID NO.:1 meets the written description provision of 35 U.S.C. § 112, first paragraph."

As an initial matter, Applicants point out that their specification does not need to describe exactly all the subject matter that is claimed. *In re Daniels*, 114 F.3d 1452, 46 U.S.P.Q.2d 1788 (Fed. Cir. 1998); *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 227 U.S.P.Q. 117 (Fed. Cir. 1985). Applicants need only communicate to those skilled in the art that the claimed subject matter is intended to be part of their invention. As stated by the Federal Circuit in *Martin v. Mayer*, 823 F.2d 500, 3 U.S.P.Q.2d 1333 (Fed. Cir. 1987):

> "[T]he specification must 'convey clearly to those skilled in the art to whom it is addressed...the information that [the inventor] has invented the specific subject matter later claimed.'

Moreover, the M.P.E.P. § 2163.02 (Eighth Edition, August 2001) states:

> [A]n objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed."

In applying this standard, the Federal Circuit has held that the specification must convey with reasonable clarity to a skilled artisan that the inventor "was in possession of the invention" at the time of filing. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). Moreover, in *Lilly*, the Federal Circuit acknowledged that "every species in a genus need not be described in order that a genus meets the written description requirement." 43 U.S.P.Q.2d at 1405 (citing *Utter v. Hiraga*, 845 F.2d 993, 6 U.S.P.Q.2d 1709 (Fed. Cir. 1988) ("A specification may, within the meaning of § 112, ¶ 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses.") Applicants have plainly met these standards since their specification would certainly indicate to one of ordinary skill in the art that Applicants discovered that alterations in the Sal2 nucleic acid, reduced Sal2 protein levels, or the presence of an altered Sal2 protein would identify a mammal as having or being at risk of acquiring a proliferative associated-disease. Applicants submit that the scope of Claim 1, as amended, is sufficiently described in the specification to satisfy the standards of Written Description guidelines.

Claim 1, as amended, is directed to a method of identifying a mammal having or at risk of acquiring a proliferative disorder by performing at least one of the following steps: 1) measuring Sal2 protein levels; 2) determining the presence or absence of an altered Sal2 protein; or 3) determining the presence or absence of a proliferative disease-associated alteration in a Sal2 nucleic acid. Applicants' specification clearly describes the presently claimed methods. For the following reasons, this rejection should be

withdrawn.

The Examiner asserts that "the specification fails to provide evidence of other alterations associated with a tumor or a proliferative disease, the specification fails to disclose any abnormal pattern(s) of SNP and RFLP in any proliferative-associated disease." Applicants disagree.

First, Applicants direct the Examiner's attention to Figure 11 of the application, described in further detail on pages 36 and 37 of the specification, in which a RFLP analysis was performed comparing DNA isolated from matched normal and ovarian tumor tissues. While digestion with the restriction enzyme MboII of a Sal2 nucleic acid corresponding to a 73S (or wild type allele) resulted in the production of three distinct fragments as detected by gel electrophoresis, digestion of the aberrant Sal2 nucleic acid having a 73C allele, on the other hand, only yielded two fragments. Thus, Applicants clearly provide evidence of abnormal patterns as detected by RFLP in a proliferative-associated disease, namely ovarian cancer.

Secondly, contrary to the Examiner's assertion that only one alteration is provided by the present invention, Applicants respectfully submit that a representative number of species of altered Sal2 nucleic acid is in fact provided by the present specification. In addition to the S73C mutation, Applicants note that the specification also discloses the G744R mutation (page 36, line 28), which was detected by screening of ovarian carcinoma cell lines. In the Declaration of Dr. Thomas Benjamin submitted herewith, Dr. Benjamin also presents data confirming the presence of this mutation in human patients having ovarian cancer (see exhibit 1). "Page 36 (line 28) of the specification also discloses of a G744R substitution in ovarian carcinoma cell lines, which we have also found in human ovarian tumor samples." Furthermore, Dr. Benjamin also states that other polymorphisms of the *Sal2* gene have been detected in ovarian cancer. Such a polymorphism is found, for example, at amino acid position 120, and is characterized by the presence of a serine (S) or a proline (C) residue. While healthy tissues screened for

> remained constant, over the past 30 years, at approximately 15%. Conversely, those women diagnosed with cancer confined to the ovary (stage I) have an overall 5-year survival approaching 90%. Clearly, the need for early detection of ovarian cancer is the best way to improve survival.

Applicants therefore submit that, based on Applicant's discovery of Sal2 alterations, the screening methods of the present invention would therefore be particularly useful for the prevention of proliferative diseases, such as cancer. Although Sal2 defects do not affect 100% of all ovarian cancer patients, the Examiner even acknowledges that "no single gene has been shown to participate in the development of all, or even the majority of human cancers." As Dr. Benjamin states in his Declaration enclosed herewith, none of the healthy tissues screened were ever found to be homozygous for the aberrant genetic alteration or the 73C allele. These data strongly suggests that any loss of heterozygosity (LOH), a characteristic inherent to tumor suppressor genes, would only occur in tumors. Accordingly, as shown in Figure 11 and described on pages 36 and 37 of the specification, Applicants have demonstrated LOH in an ovarian tumor sample from a patient having ovarian cancer, while the corresponding normal tissue was heterozygous for both the 73C and 73S alleles. Based on the correlation found between defects in Sal2, at the protein or genetic level, and proliferative diseases, one skilled in the art would immediately understand that the presence of any defect in Sal2 would identify a mammal as having or at risk of having cancer.

Given the wide expression of Sal2 in humans (see, for example, Figure 6), it is furthermore expected that any defect in Sal2 in other tissues other than the ovaries would similarly correlate with a mammal having or being at risk of acquiring a proliferative disease. In this regard, the specification teaches, for example, on pages 34 and 35 that human Sal2 gene has been mapped to chromosome 14q12, a region associated with LOH in 49% of ovarian cancers and about 25% of bladder cancers. Applicants again point to the enclosed Declaration by Dr. Benjamin, in which Dr. Benjamin states that $p150^{Sal2}$, a

this polymorphism were heterozygous for both residues (S/P), the finding that *only* tumor tissues were homozygous (C/C) strongly suggests the involvement of this polymorphism in ovarian cancer.

The Examiner further asserts that "a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of *altered Sal2* that are "associated with a proliferative disease." Applicants disagree and submit that one skilled in the art reading the specification would understand that any defect in Sal2 would identify a mammal as having or being at risk of acquiring a proliferative disease and would therefore clearly understand the scope of the claimed invention for the following reasons.

In light of the present amendment, the claimed invention now encompasses other alterations in Sal2. The specification provides multiple representative species of the genus of Sal2 defects correlating with a proliferative disease, which include alterations in the *Sal2* nucleic acid, a reduction in Sal2 protein levels, or the presence of an altered Sal2. Such defects are found in up to 80% of tumor patient samples and are described in detail, for example, in Figure 7 and Table 3, page 20 (lines 30 and 31) and page 36 of the specification.

Based on the specification, a strong correlation clearly exists between defects in Sal2 and a proliferative disorder because Sal2 defects affect a large proportion of patients surveyed having ovarian cancer. Applicants further note that the screening methods of the current invention are particularly useful in the detection and treatment of cancers, such as ovarian cancer, to avoid high mortality rates. For example, the Internet website http://www.drdonnica.com/guests/00001174.htm states that:

> The majority of women with ovarian cancer (75%) are diagnosed after the disease has reached an advanced stage (stage III or IV) because the symptoms of ovarian cancer are vague or "silent". Despite aggressive surgical intervention and new chemotherapeutic regimens, the overall 5-year survival rate for women with advanced stage ovarian cancer has

product of the Sal2 gene, is frequently down-regulated in various patient tumor samples matched with healthy tissue. Applicants demonstrate that out of 14 kidney tumor samples, at least 10 showed down-regulation in $p150^{Sal2}$ protein levels and similarly, out of 11 colon tissue samples, at least 10 showed downregulation in $p150^{Sal2}$ protein levels relative to their corresponding healthy tissue. Thus, one skilled in the art reading the specification would understand given the wide expression of Sal2, that defects in such a protein would identify a patient as having or being at risk of acquiring a broad range of proliferative diseases.

Even if, for argument's sake, the claimed invention were exemplified by a single genetic alteration (S73C of the *Sal2* gene) as is stated by the Examiner, Applicants submit that one of skill in the art reading this specification would have readily recognized that such an alteration in this gene was merely illustrative of the broader method disclosed and claimed invention. Furthermore, one skilled in the art would also understand that Applicants' invention included <u>any</u> alteration in the Sal2 nucleic acid, or any alteration in the Sal2 protein which would ultimately result in a reduction in the expression of a Sal2 protein, the expression of an altered form of the protein, or any alterations in the *Sal2* nucleic acid. It is this description that clearly conveys Applicants' invention to those persons of skill in the art. This description also allows the skilled worker to identify and recognize other species falling within the present claims. Clearly, based on this description, one skilled in the art would recognize that at the time of filing, Applicants' invention encompassed—not a single genetic alteration of the *Sal2* gene—but any alteration either at the nucleic acid or protein level of Sal2, and, on this basis alone, the written description rejection may be withdrawn.

Moreover, Applicants submit that their specification provides a written description of the presently claimed invention in sufficient detail to satisfy the standard set by the Federal Circuit in *Lilly*, 43 U.S.P.Q.2d 1398. In particular, this case specifically states that the written description of a genus of DNA may be achieved by a "recitation of

structural features common to members of the genus." *Lilly*, 43 U.S.P.Q.2d 1398, 1406. Applicants point out that, contrary to the assertion in the present Office Action, the description of the claimed invention in Applicants' specification does not rely simply on the disclosed genetic alteration of the Sal2 gene. Rather, the present specification describes any defect at the genetic or protein level, which affect Sal2. Applicants' specification therefore provides a description of the class of Sal2 defects encompassed by the present claims in a form entirely consistent with the standard set out in *Lilly*.

Overall, Applicants have sufficiently provided representative species for Sal2 defects as required by the limitations of the claimed invention. Overall, one skilled in the art reading the specification would understand the strong correlation with defects in Sal2 both at the protein and genetic level, with having or being at risk of having a proliferative disorder, including ovarian cancer. Thus, in view of Applicant's specification, one skilled in the art would understand what is encompassed by the present claims. There can be no question that applicants were in possession of the claimed genus at the time their application was filed, and that one skilled in the art would recognize applicants' disclosure as a description of the invention defined by the present claims. As a result, applicants' specification clearly satisfies the written description requirement, as set forth by the case law and the M.P.E.P., and applicants request reconsideration and withdrawal of this basis for the § 112 rejection.

Enablement

Claims 1-12

Claims 1-12 also stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The Examiner states that while the specification is

> "enabling for detecting the S730 point mutation in the *Sal2* gene, does not reasonably provide enablement for identifying a mammal having or at increased risk of acquiring a (any) proliferative disease. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims."

As a first matter, the Examiner states that the specification teaches that while the majority (17/20) are negative for $p150^{Sal2}$ expression and show no evidence of loss or gross rearrangement of the hSal2 locus, only 15% of all samples had a genetic alteration (S73C) of the Sal2 gene. Thus, the Examiner concludes that the "data collected only reflect a small number of certain type of proliferative disease" and that the specification is not enabled since it fails to teach the status of hSal2 gene in other proliferative diseases and to establish the S73C point mutation of the Sal2 gene and any other proliferative disease.

Applicants first note, referring to Figure 7 and Table 3, that only 10 not 17 tumors were actually negative for $p150^{Sal2}$ expression. As is stated above, the present claim, as amended, is drawn to the detection of any defect in Sal2 either at the nucleic acid or protein level to identify a mammal as having or at risk of having a proliferative disease. The defects encompassed by the claimed invention were found in the vast majority of tumor samples tested. Applicants direct the Examiner to Figure 7 (further summarized in Table 3), which shows $p150^{Sal2}$ expression in 20 human ovarian tumor samples. Applicants note that "[A]pproximately 80% of the tumors examined were negative or showed altered or reduced patterns of expression by Western analysis (page 20 (lines 30 and 31)). Since Sal2 is widely expressed in human tissues, as demonstrated in Figure 6, it is expected that such defects in Sal2, at the genetic or protein level, would not exclusively result in proliferative diseases of the ovary, but would identify a mammal having or being at risk of acquiring any proliferative disease. Applicants further refer to the Declaration by Dr. Benjamin, in which it is confirmed that Sal2 protein expression is markedly reduced in the large majority of kidney and colon tumor samples tested. Accordingly, the identification of defects in Sal2 at the nucleic acid and protein level identifies a mammal

as having or being at risk of having any proliferative disease, including ovarian cancer. Thus, defects in Sal2 from the claimed invention, including alterations in the *Sal2* gene, the presence of altered Sal2 proteins, or the reduced expression of the Sal2 protein, are not rare events, and do not "reflect a small number of a certain type of proliferative disease." Applicants therefore submit that the specification is enabled for the scope of the present claims.

The Examiner further asserts that an enabled diagnostic or prognostic method should be able to provide a requisite standard from the alteration of Sal2 gene for identifying a mammal having or at increased risk of acquiring a proliferative disease and that such "a standard could be obtained by providing insight to various changes in the Sal2 gene and how they are associated with certain types of proliferative diseases." Applicants submit that such as standard is provided by the claimed invention. Claim 1, as amended, is directed to multiple changes in Sal2, including alterations in the *Sal2* gene, reduction in Sal2 protein expression as well as the presence of altered forms of the Sal2 protein. As discussed above and as shown, for example, in Figure 7 and Table 3, approximately 80% of all patients tested had a defect in Sal2, whether at the genetic or protein level, thus providing a strong association between defects in Sal2 and proliferative disorders. Consequently, the specification clearly enables one skilled in the art to identify a patient as having or being at risk of having a proliferative disease.

The Examiner is further referred to the case of *In re Wands* (858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988)), which sets forth the CAFC standard for enablement in the biotechnology arts. *Wands* holds that an invention is enabled so long as the teaching of the specification provides the invention without undue experimentation. *Wands* states that:

> the test [for determining whether experimentation is undue] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the

experimentation should proceed (emphasis added).

Applying this standard to the present case, it is clear that applicants' specification satisfies this first test outlined by the CAFC in *Wands*. According to *Wands*, a considerable amount of experimentation is permissible, if it is merely routine. Looking to applicants' situation, any "experimentation" involved in determining Sal2 defects falling within the present claims, including the identification of Sal2 protein levels, the presence of alterations in the *Sal2* gene, and the presence of altered forms of Sal2 proteins, for example, is straightforward, and is rendered so by applicants' discovery that such defects identify a mammal as having or being at risk of a proliferative disease. All that would be required for one skilled in the art would be to test a mammal for at least one of the following steps: 1) measuring Sal2 protein levels in a cell of a mammal and determining if such a level is reduced relative to a control cell not having or not being at risk of having or being at risk of a proliferative disease; 2) determining the presence or absence of an altered Sal2 protein relative to a Sal2 protein in a mammal not having or not being at risk of a proliferative disease; or 3) determining the presence or absence of a genetic alteration in the *Sal2* gene relative to the sequence of SEQ ID NO.:2 and 4. Such steps can be routinely determined by standard techniques in the art and are described, for example, in the specification on pages 18-20. Given the strong correlation between Sal2 defects and proliferative diseases as well as the wide expression of Sal2 in human tissues, it would not require undue experimentation for one skilled in the art to determine Sal2 defects in other tissues in order to identify a mammal as having or being at risk of having any proliferative disease. These approaches would require only standard techniques of molecular biology None of the aforementioned steps constitutes undue experimentation. Accordingly, there is no basis for concluding that one skilled in the art, equipped with applicants' teachings and standard methods known in the art, would not be able to identify a mammal having or being at risk of having a proliferative disease according to the identification of Sal2 defects which fall within the scope of the present claims.

Alternatively, applying the second test of *Wands*, a "reasonable amount of guidance" is also provided by applicants' specification. For example, Applicants outline general methods useful for identifying Sal2 defects (see pages 18-21). Applicants show for example on page 20 (lines 11-14) that Sal2 protein expression can readily be determined by standard techniques, such as ELISA, Western Blot, or RIA. Furthermore, Applicants also show in Figure 6 that Sal2 is a widely expressed protein in human tissues. In view of such teachings, Applicants submit that the present specification certainly provides guidance for the detection of Sal2 defects in any tissue to identify a mammal as having or being at risk of a proliferative disease and that this teaching, in and of itself, is more than adequate to satisfy the requisite "reasonable amount of guidance." Accordingly, based on this second test as well, applicants submit that the present specification is within the bounds set out by *Wands* for an enabling disclosure.

Applicants also note that as the case of *In re Wands* (858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988)) makes clear, enablement is not negated by the necessity for some experimentation such as screening of alterations of the *Sal2* gene. The nature of molecular biology and its application to cancer biology is that it involves screening of multiple genetic alterations to determine which specific alteration within the sequence of a particular tumor suppressor identifies a mammal as having or being at risk of a proliferative disease. Like the practitioners of the monoclonal antibody art described in *Wands*, who screened many hybridomas to isolate the one having the desired characteristics, practitioners in the art of molecular biology would routinely screen alterations in the *Sal2* gene and the Sal2 protein to determine defects associated with a proliferative disease without undue experimentation. Any "experimentation" involved would be entirely straightforward and routine. Applicants therefore maintain that their specification satisfies the enablement standard under, not one, but both of the alternative tests set forth by *Wands*.

Overall, the invention provides convincing data supporting the link between

aberrant Sal2 expression (at the nucleic acid level, protein level, or both) and proliferative diseases. Clearly, the specification enables the scope of the present claims. The teachings of the specification are applicable to various types of proliferative diseases and the specification also teaches multiple defects of Sal2, both in normal and in disease tissues, to enable one skilled in the art to identify a mammal having or being at risk of acquiring such diseases. Accordingly, all that is required is for one skilled in the art to test for such defects, using standard techniques in the art, to identify a mammal as having or at risk of having a proliferative disease in the absence of undue experimentation. Thus, the § 112, first paragraph rejection should be withdrawn.

Claims 7-12

Based on claims 7-12, which provide a method of determining the alteration in Sal2 gene by *in situ* hybridization using a nucleic acid probe specific for the gene alteration, the Examiner finds that the Specification fails to provide sufficient guidance with regard to whether such small gene alteration could be detected by this method. In particular, the Examiner states that "the alteration taught only differs in one nucleic acid base (TSGT for TACT), the specification fails to provide sufficient guidance with regard to whether such small gene alteration could by detected by *in site* [sic] hybridization method."

Applicants submit that various methods used routinely in the art can detect single allelic changes, including for example, single nucleotide polymorphism (SNP determination). Such methods are described, for example, on pages 3, 18, and 19 of the specification. Page 3 of the specification clearly states:

> "...determining whether the mammal has or is at increased risk of acquiring a proliferative disease is done by, for example, polymerase cahin reaction (PCR) amplification, single nucleotide polymorphism (SNP) determination..." (emphasis added)

These methods are also described, for example, in PCT WO00/50869. A similar

technique is also described, for example, by Watson et al. (*Recombinant DNA,* Scientific American Books, New York, NY, 1992, pages 550-551). This method employed

> "for looking directly for a mutation uses probes that are designed to hybridize selectively to either the normal or the mutant allele. These *allele-specific oligonucleotide* probes (or ASOs) can be used for any disorder where the nucleotide sequence of the mutant and normal alleles are known."

Furthermore, these probes, as claimed herein, are "used as probes to distinguish the normal and mutant sequences by changing the stringency of hybridization to a level at which each of the oligonucleotides will anneal stably only to the sequence to which it is perfectly complementary and not to the sequence with which it has the single mismatch."

The M.P.E.P. clearly states in the Guidelines for the Examination of Patent Applications under 35 U.S.C. § 112, first paragraph, "Enablement" requirement:

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject manner sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi,* 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370.

Thus, Applicants submit that claims 7-12 are enabled and in the absence of evidence of the contrary, Applicants respectfully request that this rejection of claims 7-12 be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-12 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

In particular, the Examiner asserts that there is no positive step in claim 1 which recites how the alteration is to be determined. Applicants note that the present amendment to claim 1 renders this rejection moot. This aspect of the rejection should therefore be withdrawn.

The Examiner further finds that Claim 7 is indefinite because the limitation "said human Sal2 gene" lacks antecedent basis. Claim 7 has been amended to clarify the claim language. This rejection may now be withdrawn.

INFORMATION DISCLOSURE STATEMENT

Applicants note that the Form PTO-1449 that was submitted with an Information Disclosure Statement filed on February 26, 2002 has not been initialed and returned, and hereby request that it be initialed and returned with the next Office Action.

CONCLUSION

Applicants submit that the application is in condition for allowance and such action is respectfully requested.

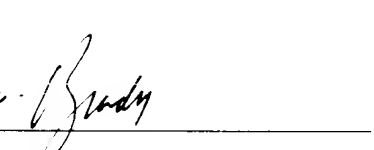
Enclosed are "marked-up" and clean versions of the claims and replacement paragraphs.

Also enclosed is a Petition to extend the period for replying to the Office Action for three months, to and including February 14, 2003, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: February 14, 2003



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Version of Claims and Replacement Paragraphs Showing Changes Made

Please replace the paragraph starting on line 28 of page 3 with the following paragraph.

> A further aspect of the invention encompasses a knockout mouse featuring a knockout mutation in a genomic mouse *Sal2* (*mSal2*) gene. This knockout mouse may also contain, for example, a nucleic acid construct including a mutant *Sal2* gene and this mutant Sal2 gene may be conditionally expressed. In a preferred embodiment, the mutant *Sal2* gene, for example a human *Sal2* gene, encodes a protein that contains a substitution of a Cys for the Ser at position 73 of SEQ ID NO.:1. However, the Sal2 protein may also be wild-type.

Please replace the paragraph starting on line 27 of page 34 with the following paragraph.

> The *hSal2* gene has been mapped to chromosome 14q12 but was not recognized initially as a tumor suppressor gene. It was subsequently shown by others that this region of 14q is associated with a loss of homozygosity in 49% of ovarian cancers (Bandera et al., *supra*) and about 25 % of bladder cancers (Chang et al., *supra*). These findings, along with the underlying rationale of 'tumor host range' selection, suggest the possibility that *sal2* may function as a tumor suppressor. To test this possibility more directly, a screen for $p150^{sal2}$ expression was carried out on extracts of ovarian carcinomas (Fig. 7). Fig. 7 shows a Western blot of human ovarian tumors. The expression level of $p150^{sal2}$ in 20 ovarian carcinomas was compared with that of normal ovarian epithelial cells (N) [in two panels]. Fifty micrograms of protein were loaded in each lane and blotted with polyclonal antibody against $p150^{sal2}$. Each ovarian carcinoma was labeled by its case number. Arrows indicate the normal position of p150. A polyclonal anti-p150 antibody made against the mouse protein clearly recognizes the human protein (Fig. 3B above). A band

of the same apparent molecular weight is seen in extracts of normal human ovarian epithelial cells ('HOSE').

1. (Amended) A method of identifying a mammal having or at risk of acquiring a proliferative disease, said method comprising [the step of] at least one of the following steps:

(a) measuring the Sal2 protein level in a cell of said mammal relative to the Sal2 protein level in a mammal not having or being at risk for said proliferative disease;

(b) determining the presence or absence of an altered Sal2 protein in said mammal relative to a Sal2 protein in a mammal not having or being at risk for a said proliferative disease; or

(c) determining [whether there is] the presence or absence of a proliferative disease-associated alteration in a *Sal2* nucleic acid [of] in said mammal relative to the nucleic acid sequence of SEQ ID NO.: 2 and SEQ ID NO.:4, wherein a decrease in said SAL2 protein level in step (a) or the presence of an alteration in steps (b) or (c) identifies a mammal as having or being at risk of acquiring a proliferative disease.

7. (Amended) The method of claim 1, wherein [said method] step (c) comprises the steps of:

(i) contacting a first nucleic acid probe which is specific for binding to a [said] human *Sal2* nucleic acid containing [said] a proliferative disease-associated alteration with a nucleic acid from a cell from said mammal under conditions which allow said first nucleic acid probe to anneal to complementary sequences in

said cell; and

(ii) detecting duplex formation between said first nucleic acid probe and said complementary sequences.